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(57) Abstract

Lightly crosslinked polymers, preferably ones prepared by suspension or emulsion polymerizing at least about 90 % by weight of a carboxyl-containing monoethylenically unsaturated monomer such as acrylic acid with from about 0.1 % to about 5 % by weight of a polyfunctional, and preferably difunctional, crosslinking agent such as divinyl glycol (3,4-dihydroxy-1,5-hexadiene), having a particle size of not more than about 50 μm in equivalent spherical diameter, when formulated with an ophthalmic medicament, e.g., fluorometholone, into suspensions in aqueous medium in which the amount of polymer ranges from about 0.1 % to about 6.5 % by weight, based on the total weight of the aqueous suspension, the pH is from about 3.0 to about 6.5, and the osmotic pressure (osmolality or tonicity) is from about 10 mOsM to about 400 mOsM, provide new topical ophthalmic medicament delivery systems having suitably low viscosities which permit them to be easily administered to the eye in drop form, and hence be comfortably administrable in consistent, accurate dosages. These suspensions will rapidly gel in the eye after coming into contact with the eye's tear fluid to a substantially greater viscosity than that of the originally-introduced suspension and thus remain in place for prolonged periods of time to provide sustained release of the ophthalmic medicament.

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OPHTHALMIC SUSPENSIONS

REFERENCE TO RELATED APPLICATION

This application is a continuation-in-part of copending application Serial No. 153,762 filed February 8, 1988.

FIELD OF THE INVENTION

This invention relates to new topical ophthalmic medicament delivery systems and to methods of preparing them. More particularly, this invention relates to new topical ophthalmic medicament delivery systems comprising aqueous suspensions of particular lightly crosslinked polymers of acrylic acid or the like, which suspensions also contain an ophthalmic medicament. Such suspensions are easily administrable to the eye in drop form, and hence can be administered by or to a patient with a greater degree of comfort than either hitherto available petrolatum-based ophthalmic ointments or ophthalmic formulations containing the same or similar polymers in the form of aqueous, highly viscous gels or anhydrous suspensions or emulsions. The novel aqueous suspensions of this invention, once they have been dropped into the eye, come into contact with the eye's tear fluid, rapidly gel in situ to a substantially greater viscosity than that of the originally-introduced suspension and remain in place for prolonged periods of time. Sustained release of the medicament contained in the suspension - and now entrapped within the more viscous gel formed in the eye - then takes place.

BACKGROUND OF THE INVENTION

Medicaments have been administered to the eye in eyedrops, ointments or creams, in gelatin lamellae or other biologically soluble or insoluble films or sheets, by dispensing ocular inserts, as suspensions or emulsions in non-aqueous vehicles and in highly viscous aqueous gels. The disadvantages associated with each of these ophthalmic drug delivery systems are well known. Eyedrops in the form of aqueous solutions or suspensions are rapidly washed away by the eye's tear fluid. Ointments or creams blur the vision, and also have comparatively short residence times in the eye. Gelatin lamellae or other films or sheets, ocular inserts and non-aqueous suspensions and emulsions all can cause immediate pain and continuing discomfort and can also interfere with vision. Highly viscous aqueous gels, such as those disclosed in Schoenwald et al. U.S. Patents Nos. 4,271,143 and 4,407,792, issued June 2, 1981 and October 4, 1983, respectively, are difficult to administer so as to provide consistent, accurate dosages and may be uncomfortable to administer as well.

The Schoenwald et al. patents disclose that crosslinked carboxyl-containing polymers of the same general type as those employed in practicing this invention can be used in their ophthalmic drug delivery systems. Such systems are, however, formulated as either highly viscous aqueous gels or anhydrous suspensions and administered in those forms. Neither acrylic acid polymer-containing ophthalmic drug delivery systems formulated as aqueous suspensions capable of being administered in dropwise fashion nor any means by which such aqueous suspensions could be prepared are disclosed in the Schoenwald et al. patents.

A controlled release treatment composition that may be placed in the precorneal pocket of the eye containing a treating agent and a "bioadhesive" is

disclosed in Robinson, U.S. Patent No. 4,615,697, issued October 7, 1986. The bioadhesive is described as a water-swellable, although water-insoluble, fibrous, cross-linked carboxy-functional polymer with a plurality of repeating units in which about at least 80 percent thereof contain at least one carboxy functionality and a cross-linking agent (0.05 to 1.5 percent) that is substantially free of polyalkenyl polyether. The bioadhesive is sized to, at the maximum, to pass through a sieve screen having a 10 mesh (U.S. Standard Sieve Series), that is, a 2000 micron opening, to minimize visual impairment. The viscosity, osmolality, and pH of the composition are not indicated.

An ophthalmic gel composition that is an aqueous solution of a carboxy vinyl polymer, a water-soluble basic substance, and an ophthalmic drug is taught in Toko Yakuhin Kogyo K.K., United Kingdom Patent Application GB 2,007,091A, published May 16, 1979. The gel has a pH of 5 to 8 and a viscosity of 1,000 to 100,000 centipoises at 20°C. It is stated that adding a small amount of sodium chloride or an aqueous solution thereof to the gel causes it to convert to a liquid with a great reduction in viscosity. Contact with tear fluid will cause also a great reduction in viscosity.

It is therefore an object of this invention to provide new topical ophthalmic medicament delivery systems.

It is also an object of this invention to provide new topical ophthalmic medicament delivery systems that are easily administrable to the eye in drop form.

A further object of this invention is to provide new topical ophthalmic medicament delivery systems that are easily administrable in drop form and which comprise aqueous suspensions of particular lightly crosslinked polymers of acrylic acid or the like containing an ophthalmic medicament.

Yet another object of this invention is to provide new topical ophthalmic medicament delivery systems that are easily administrable in drop form and, after coming into contact with the eye's tear fluid, rapidly gel in the eye to a substantially greater viscosity than the viscosity of the administered drop.

A still further object of this invention is to provide methods of preparing these new topical ophthalmic medicament delivery systems.

An additional object of this invention is to provide a method of administering new topical ophthalmic medicament delivery systems that are easily administrable in drop form, which method encompasses the treatment of "dry eye" by supplementing tear fluid.

These and other objects, as well as the nature, scope and utilization of this invention, will become readily apparent to those skilled in the art from the following description and the appended claims.

SUMMARY OF THE INVENTION

Lightly crosslinked polymers containing predominantly carboxyl-containing monomers, such as Carbopol (trademark, The B.F. Goodrich Company) polymers, and preferably ones prepared by suspension or emulsion polymerizing acrylic acid or the like and a crosslinking agent such as divinyl glycol (3,4-dihydroxy-1,5-hexadiene) or the like to an average dry particle size of not more than about 50 μm in equivalent spherical diameter, are formulated with an ophthalmic medicament into suspensions in aqueous medium in which the amount of polymer, the pH, and the osmotic pressure (osmolality or tonicity) are within the ranges given hereinbelow. Such suspensions provide topical ophthalmic medicament delivery systems having suitably low viscosities that permit them to be easily administered to the eye in drop form, and hence be comfortably administrable in

consistent, accurate dosages. These suspensions rapidly gel in the eye after coming into contact with the eye's tear fluid to a substantially greater viscosity than that of the originally-introduced suspension and thus remain in place over prolonged periods of time to provide comfortable and sustained release of the ophthalmic medicament.

DETAILED DESCRIPTION OF THE INVENTION

The lightly crosslinked polymers of acrylic acid or the like used in practicing this invention are, in general, well known in the art. In a preferred embodiment such polymers are ones prepared from at least about 90%, and preferably from about 95% to about 99.9% by weight, based on the total weight of monomers present, of one or more carboxyl-containing monoethylenically unsaturated monomers. Acrylic acid is the preferred carboxyl-containing monoethylenically unsaturated monomer, but other unsaturated, polymerizable carboxyl-containing monomers, such as methacrylic acid, ethacrylic acid, β-methylacrylic acid (crotonic acid), cis-α-methylcrotonic acid (angelic acid), trans-α-methylcrotonic acid (tiglic acid), α-butylcrotonic acid, α-phenylacrylic acid, α-benzylacrylic acid, α-cyclohexylacrylic acid, β-phenylacrylic acid (cinnamic acid), coumaric acid (o-hydroxycinnamic acid), umbellic acid (p-hydroxycoumaric acid), and the like can be used in addition to or instead of acrylic acid.

Such polymers are crosslinked by using a small percentage, i.e., from about 0.1% to about 5%, and preferably from about 0.2% to about 1%, based on the total weight of monomers present, of a polyfunctional crosslinking agent. Included among such crosslinking agents are non-polyalkenyl polyether difunctional crosslinking monomers such as divinyl glycol; 2,3-dihydroxyhexa-1,5-diene; 2,5-dimethyl-1,5-hexadiene;

divinylbenzene; N,N-diallylacrylamide; N,N-diallylmethacrylamide and the like. Also included are polyalkenyl polyether crosslinking agents containing two or more alkenyl ether groupings per molecule, preferably alkenyl ether groupings containing terminal $H_2C=C<$ groups, prepared by etherifying a polyhydric alcohol containing at least four carbon atoms and at least three hydroxyl groups with an alkenyl halide such as allyl bromide or the like, e.g., polyallyl sucrose, polyallyl pentaerythritol, or the like; see, e.g., Brown U.S. Patent No. 2,798,053. Diolefinic non-hydrophilic macromeric crosslinking agents having molecular weights of from about 400 to about 8,000, such as insoluble di- and polyacrylates and methacrylates of diols and polyols, diisocyanate-hydroxyalkyl acrylate or methacrylate reaction products, and reaction products of isocyanate terminated prepolymers derived from polyester diols, polyether diols or polysiloxane diols with hydroxyalkylmethacrylates, and the like, can also be used as the crosslinking agents; see, e.g., Mueller et al. U.S. Patents Nos. 4,192,827 and 4,136,250.

The lightly crosslinked polymers can of course be made from a carboxyl-containing monomer or monomers as the sole monoethylenically unsaturated monomer present, together with a crosslinking agent or agents. They can also be polymers in which up to about 40%, and preferably from about 0% to about 20% by weight, of the carboxyl-containing monoethylenically unsaturated monomer or monomers has been replaced by one or more non-carboxyl-containing monoethylenically unsaturated monomers containing only physiologically and ophthalmologically innocuous substituents, including acrylic and methacrylic acid esters such as methyl methacrylate, ethyl acrylate, butyl acrylate, 2-ethyl-hexylacrylate, octyl methacrylate, 2-hydroxyethyl-methacrylate, 3-hydroxypropylacrylate, and the like, vinyl acetate, N-vinylpyrrolidone, and the like; see Mueller et al. U.S.

Patent No. 4,548,990 for a more extensive listing of such additional monoethylenically unsaturated monomers. Particularly preferred polymers are lightly crosslinked acrylic acid polymers wherein the crosslinking monomer is 2,3-dihydroxyhexa-1,5-diene or 2,3-dimethylhexa-1,5-diene.

The lightly crosslinked polymers used in practicing this invention are preferably prepared by suspension or emulsion polymerizing the monomers, using conventional free radical polymerization catalysts, to a dry particle size of not more than about 50 μm in equivalent spherical diameter; e.g., to provide dry polymer particles ranging in size from about 1 to about 30 μm, and preferably from about 3 to about 20 μm, in equivalent spherical diameter. In general, such polymers will range in molecular weight estimated to be about 250,000 to about 4,000,000, and preferably from about 500,000 to about 2,000,000.

Aqueous suspensions formulated in accordance with this invention containing polymer particles prepared by suspension or emulsion polymerization whose dry particle size is appreciably larger than about 50 μm in equivalent spherical diameter are less comfortable when administered to the eye than suspensions otherwise identical in composition containing polymer particles whose equivalent spherical diameters are, on the average, below about 50 μm. It has been discovered, furthermore, that lightly crosslinked polymers of acrylic acid or the like prepared to a dry particle size appreciably larger than about 50 μm in equivalent spherical diameter and then reduced in size, e.g., by mechanically milling or grinding, to a dry particle size of not more than about 50 μm in equivalent spherical diameter do not work as well as polymers made from aqueous suspensions as taught by this invention. While we do not wish to be bound by any theory or mechanism advanced to explain the functioning of this invention, one possible explanation

for the difference of such mechanically milled or ground polymer particles as the sole particulate polymer present is that grinding disrupts the spatial geometry or configuration of the larger than 50 μm lightly crosslinked polymer particles, perhaps by removing uncrosslinked branches from polymer chains, by producing particles having sharp edges or protrusions, or by producing ordinarily too broad a range of particle sizes to afford satisfactory delivery system performance. A broad distribution of particle sizes will impair the viscosity-gelation relationship. In any event, such mechanically reduced particles are less easily hydratable in aqueous suspension than particles prepared to the appropriate size by suspension or emulsion polymerization, and also are less able to gel in the eye under the influence of tear fluid to a sufficient extent and are less comfortable once gelled than gels produced in the eye using the aqueous suspensions of this invention. However, up to about 40% by weight, e.g., from about 0% to over 20% by weight, based on the total weight of lightly crosslinked particles present, of such milled or ground polymer particles can be admixed with solution or emulsion polymerized polymer particles having dry particle diameters of not more than about 50 μm when practicing this invention. Such mixtures will also provide satisfactory viscosity levels in the ophthalmic medicament delivery systems and in the <u>in situ</u> gels formed in the eye coupled with ease and comfort of administration and satisfactory sustained release of the medicament to the eye, particularly when such milled or ground polymer particles, in dry form, average from about 0.01 to about 30 μm, and preferably from about 1 to about 5 μm, in equivalent spherical diameter.

In the most preferred embodiment of the invention, the particles have a narrow particle size distribution. The use of a monodisperse particle will give maximum viscosity and an increased eye residence

time of the ophthalmic medicament delivery systems for a given particle size. Monodisperse particles having a particle size of 30 μm and below are most preferred. Good particle packing is aided by a narrow particle size distribution.

The aqueous suspensions of this invention will contain amounts of lightly crosslinked polymer particles ranging from about 0.1% to about 6.5% by weight, and preferably from about 0.5% to about 4.5% by weight, based on the total weight of the aqueous suspension. They will preferably be prepared using pure, sterile water, preferably deionized or distilled, having no physiologically or ophthalmologically harmful constituents, and will be adjusted to a pH of from about 3.0 to about 6.5, and preferably from about 4.0 to about 6.0, using any physiologically and ophthalmologically acceptable pH adjusting acids, bases or buffers, e.g., acids such as acetic, boric, citric, lactic, phosphoric, hydrochloric, or the like, bases such as sodium hydroxide, sodium phosphate, sodium borate, sodium citrate, sodium acetate, sodium lactate, THAM (trishydroxymethylamino-methane), or the like and salts and buffers such as citrate/dextrose, sodium bicarbonate, ammonium chloride and mixtures of the aforementioned acids and bases.

When formulating the aqueous suspensions of this invention, their osmotic pressure (π) will be adjusted to from about 10 milliosmolar (mOsM) to about 400 mOsM, and preferably from about 100 to about 250 mOsM, using appropriate amounts of physiologically and ophthalmologically acceptable salts. Sodium chloride is preferred to approximate physiologic fluid, and amounts of sodium chloride ranging from about 0.01% to about 1% by weight, and preferably from about 0.05% to about 0.45% by weight, based on the total weight of the aqueous suspension, will give osmolalities within the above-stated ranges. Equivalent amounts of one or more salts

made up of cations such as potassium, ammonium and the like and anions such as chloride, citrate, ascorbate, borate, phosphate, bicarbonate, sulfate, thiosulfate, bisulfite and the like, e.g., potassium chloride, sodium thiosulfate, sodium bisulfite, ammonium sulfate, and the like can also be used in addition to or instead of sodium chloride to achieve osmolalities within the above-stated ranges.

The amounts of lightly crosslinked polymer particles, the pH, and the osmotic pressure chosen from within the above-stated ranges will be correlated to give aqueous suspensions having viscosities ranging from about 1,000 to about 30,000 centipoise, and preferably from about 5,000 to about 20,000 centipoise, as measured at room temperature (about 25°C) using a Brookfield Digital LVT Viscometer equipped with a number 25 spindle and a 13R small sample adapter at 12 rpm. Such suspensions will gel on contact with tear fluid to give gels having viscosities estimated to range from about 75,000 to about 500,000 centipoise, e.g., from about 200,000 to about 300,000 centipoise, measured as above, depending on pH as observed, for example, from pH-viscosity curves. This effect is noted by observing a more viscous drop on the eye as a set cast. The cast, after setting, can be easily removed.

The viscous gels that result from fluid eyedrops delivered by means of the aqueous suspensions of this invention have residence times in the eye ranging from about 2 to about 12 hours, e.g., from about 3 to about 6 hours. The medicaments contained in these drug delivery systems will be released from the gels at rates that depend on such factors as the drug itself and its physical form, the extent of drug loading and the pH of the system, as well as on any drug delivery adjuvants, such as ion exchange resins compatible with the ocular surface, which may also be present. For fluorometholone, for example, release rates in the rabbit eye in excess of

four hours, as measured by fluorometholone contained in the aqueous humor, have been observed.

Medicaments -- substances used in treating or ameliorating a disease or medical condition -- including drugs intended to treat therapeutically the eye itself or the tissues surrounding the eye and drugs administered via the ophthalmic route to treat therapeutically a local condition other than one involving the eye, will typically be incorporated in the topical delivery systems of this invention in therapeutically active amounts comparable to amounts administered in other dosage forms, usually in amounts ranging from about 0.005% to about 10% by weight, and preferably from about 0.01% to about 5% by weight, based on the total weight of the formulation. Thus, for example, from about 0.01% to about 1% by weight of the anti-inflammatory steroid fluorometholone can be administered in this manner.

An illustrative but by no means exhaustive listing of such medicaments includes antibiotics, antivirals, steroids, including anti-inflammatory agents, peptides, polypeptides, cardiotonics, antihypertensives, antiallergics, alpha- and beta-adrenergic blocking agents, ophthalmic medicaments such as anticataract agents, antiglaucoma agents and ophthalmic anti-inflammatory agents, ophthalmic lubricating agents, ophthalmic topical or regional anesthetic agents, etc. Specific medicaments that can be used in the present invention include drugs such as pilocarpine, idoxuridine, carbachol, bethanechol, timolol, atenolol, labetolol, metoprolol, nadolol, oxprenolol, pindolol, sotalol, betaxolol, acebutolol, alprenolol, levo-bunolol, p-aminoclonidine, dipivefrin, tetracycline, epinephrine, phenylephrine, eserine, phospholine, aceclidine, demecarium, cyclopentolate, homatropine, scopolamine, nitroglycerin, ethacrynic acid, furosemide, amiloride, chlortetracycline, bacitracin, neomycin, polymyxin, polymyxin B, gramicidin, oxytetracycline,

chloramphenicol, gentamycin, penicillins, erythromycin, sulfacetamide, tobramycin, trospectomycin, vancomycin, ciprofloxacin, perfloxacin, olfloxacin, enoxacin, naphazoline hydrochloride, clindamycin, isofluorophate, fluorometholone, dexamethasone, hydrocortisone, fluorocinolone, medrysone, prednisolone, prednisolone acetate, methylprednisolone, fluticasone propionate, betamethasone, triamcinolone, estradiol, ibuprofen, flurbiprofen, naproxen, esters of ibuprofen, flurbiprofen, and naproxen; ketorolac, suprofen, interferons, cromolyn, gancyclovir, aminozolamide, all-trans-retinoic acid (Vitamin A) and the nontoxic, pharmaceutically acceptable salts thereof. Pro-drug counterparts are also within the scope of the present invention. Ophthalmic lubricating agents are materials capable of inducing natural lacrimation or creating artificial lacrimation and include, for example, polyvinylalcohol, cellulose polymers such as hydroxypropyl methyl cellulose, polylactams such as polyvinylpyrrolidone and the like. "Dry eye" formulations that comprise pure water and a lightly crosslinked polymer of the type described hereinabove in an amount within the range also set forth hereinabove, hypotonic in saline and thus having the requisite osmotic pressure but at a pH of about 7.0 or less, e.g., about 6.5, are also contemplated as being within the scope of this invention. Topical or regional anesthetic agents include ones used during ophthalmic surgery or other ophthalmic procedures, such as lidocaine, cocaine, benoxinate, dibucaine, proparacaine, tetracaine, etidocaine, procaine, hexylcaine, bupivacaine, mepivacaine, prilocaine, chloroprocaine, and the like.

The term "pharmaceutically acceptable salt" refers to those salts of the parent compound that do not significantly or adversely affect the pharmaceutical properties (e.g., toxicity, efficacy, etc.) of the parent compound. Pharmaceutically acceptable salts

administerable by means of the aqueous suspensions of this invention include, for example, chloride, iodide, bromide, hydrochloride, acetate, nitrate, stearate, pamoate, phosphate and sulfate salts. It is sometimes desirable to use an appropriate salt form of the medicament that increases the water solubility or polar characteristics of the free drug.

The aqueous suspension topical ophthalmic medicament delivery systems of this invention can be formulated in any of several ways. For example the drug, the lightly crosslinked polymer particles, and the osmolality-adjusting salt can be pre-blended in dry form, added to all or part of the water, and stirred vigorously until apparent polymer dispersion is complete, as evidenced by the absence of visible polymer aggregates. Sufficient pH adjusting agent is then added incrementally to reach the desired pH, and more water to reach 100 percent formula weight can be added at this time, if necessary. Another convenient method involves adding the drug to about 95 percent of the final water volume and stirring for a sufficient time to saturate the solution. Solution saturation can be determined in known manner, e.g., using a spectrophotometer. The lightly crosslinked polymer particles and the osmolality-adjusting salt are first blended in dry form and then added to the drug-saturated suspension and stirred until apparent polymer hydration is complete. Following the incremental addition of sufficient pH adjusting agent to reach the desired pH, the remainder of the water is added, with stirring, to bring the suspension to 100 percent formula weight.

These aqueous suspensions can be packaged in preservative-free, single-dose non-reclosable containers. This permits a single dose of the medicament to be delivered to the eye one drop at a time, with the container then being discarded after use. Such containers eliminate the potential for

preservative-related irritation and sensitization of the corneal epithelium, as has been observed to occur particularly from ophthalmic medicaments containing mercurial preservatives. Multiple-dose containers can also be used, if desired, particularly since the relatively low viscosities of the aqueous suspensions of this invention permit constant, accurate dosages to be administered dropwise to the eye as many times each day as necessary. In those suspensions where preservatives are to be included, suitable preservatives are chlorobutanol, Polyquat, benzalkonium chloride, cetyl bromide, and the like.

In order that those skilled in the art can more fully understand this invention, the following examples are set forth. These examples are given solely for purposes of illustration, and should not be considered as expressing limitations unless so set forth in the appended claims.

EXAMPLE I

A pre-blend was prepared by dry-blending together 0.10 weight percent of fluorometholone (11β,17α-dihydroxy-9α-fluoro-6α-methylpregna-1,4-diene-3,20-dione), 1.25 weight percent of Carbopol 976 (formerly known as Carbopol EX 55) (a carboxyl-containing polymer prepared by suspension polymerizing acrylic acid and divinyl glycol; The B.F. Goodrich Company) having a particle size of 5 μm, and 0.15 weight percent of sodium chloride. This pre-blend was added to 80 weight percent of deionized water in a vessel and stirred at 20 rpm at about 25°C for 12 hours. At this point apparent polymer dispersion was complete as evidenced by the absence of visible polymer aggregates.

The resulting aqueous drug-containing suspension was then titrated with 10N aqueous sodium hydroxide to pH 4.53; following which additional

deionized water was added, with stirring, to bring the final formulation weight to 100 percent. The final aqueous suspension had an osmolality of approximately 50 mOsM and a viscosity of approximately 12,000 centipoise as measured at 25°C on a Brookfield Digital LVT Viscometer equipped with a number 25 spindle and a 13R small sample adapter at 12 rpm.

EXAMPLE II

Fluorometholone, 0.10 weight percent, was added to 80 weight percent of deionized water in a vessel and stirred at 50 rpm at 25°C for 24 hours to give a saturated aqueous suspension of the drug. Carbopol 976 polymer having a 5 μm particle size, 1.40 weight percent, and 0.25 weight percent of sodium chloride were blended in dry form and this blend was then added to the drug-saturated suspension, with stirring, at 20 rpm at 25°C for 12 hours.

The resulting aqueous drug-containing suspension was then titrated with 10N aqueous sodium hydroxide to pH 4.49, following which additional deionized water was stirred into the suspension to bring the final formulation weight to 100 percent. The final aqueous suspension had an osmolality of approximately 90 mOsM and a viscosity of approximately 18,000 centipoise, measured as in Example I.

EXAMPLES III - VIII

These examples relate to the preparation of "dry eye" formulations (Examples III - V) and pilocarpine hydrochloride formulations (Examples VI - VIII) of the present invention. For each example, NaCl and Carbopol 976, in the indicated weights, were dissolved in 100 g of distilled water using a mechanical mixer, after which the resulting formulation was sterilized at 121°C for 30 to 45 minutes. NaOH was then sterile-filtered to adjust the pH to the indicated range. In the pilocarpine examples, the pilocarpine hydrochloride was added by sterile filtration and the pH was adjusted following the sterilization. Carbopol 976 in all examples had a particle size of 5 μm.

Dry Eye Formulations

No.	Carbopol 976 (w/w %)	NaCl (w/w %)	pH
III	1.05	0.175	5.6-5.8
IV	1.05	0.050	5.6-5.8
V	0.80	0.600	5.6-5.8

Pilocarpine Hydrochloride Formulations

No.	Pilocarpine (w/w %)	Carbopol 976 (w/w %)	NaCl (w/w %)	pH
VI	1.0	2.0	0.1-0.9	5.2-5.8
VII	2.0	2.0	0.1-0.9	5.2-5.8
VIII	4.0	2.0	0.1-0.9	5.2-5.8

EXAMPLE IX

Various formulations were compounded to establish that the viscosity of the polymer solution is dependent on particle size. There were used Carbopol 976 and polycarbophyl, another polymer within the scope of

the present invention. Polycarbophyl, as referred to here, is a polyacrylic acid polymer lightly cross-linked with divinylglycol, meeting the compendium specifications of the United States Pharmacopeia, and was obtained as an experimental sample from The B.F. Goodrich Company.

A polycarbophyl lot was sieved to ranges of greater than 105 μm, less than 105 μm, less than 105 but greater than 75 μm, and less than 75 but greater than 45 μm. A sample was also ground to a size of less than 10 μm.

The general formulation used for all was 1.05 w/w% polymer and 0.2 w/w% NaCl with a pH of 5.2-5.6. The correlation between particle size and viscosity is shown in the following table.

Nominal Polymer Size (μm)	Viscosity (cps)+	(Dry) Particle
Carbopol 976	28,000	5
Polycarbophyl	1,080	<105
Polycarbophyl	19,800	<10
Polycarbophyl	1,800	>105
Polycarbophyl <105	2,800	>75 and
Polycarbophyl	9,200	>45 and <75
80 parts Carbopol 976/ 20 parts Polycarbophyl	19,200	5/<105
90 parts Carbopol 976/ 10 parts Polycarbophyl	22,000	5/<105

+ Measured at about 25°C using a Brookfield Digital LVT Viscometer equipped with a number 25 spindle and a 13R small sample adapter at 12 rpm.

EXAMPLE X

This example is directed to a fluoromethalone suspension within the scope of the present invention.

Fluoromethalone, 0.10 weight %, was added to 97 weight % of purified water in a vessel and stirred at high speed for 15 minutes to give a finely dispersed aqueous suspension of the drug. Carbopol 976 polymer having a dry particle size of 5 μm, 1.05 weight %, was added to the drug suspension with stirring and mixing was continued for a minimum of 15 minutes. After the 15-minute minimum time had elasped, 0.20 weight % of sodium chloride was added.

The resulting aqueous drug-containing suspension was sterilized at 121°C for 45 minutes. The suspension was cooled to about 50°C and a 10 N sodium hydroxide solution was then sterile filtered into the suspension with stirring to adjust the pH to 5.6-5.8. Additional purified water was sterile filtered into the suspension with stirring to bring the final formulation weight to 100%. The final aqueous suspension had an osmolality of approximately 150 mOsM, a viscosity of approximately 15,700 centipoise, measured at room temperature (about 25°C) using a Brookfield Digital LVT Viscometer equipped with a number 25 spindle and a 13R small sample adapter at 12 RPM, and a pH of about 5.6-5.8.

EXAMPLE XI

This example relates to a "dry eye"/tear substitute formulation.

Carbopol 976 polymer having a dry particle size of 5 μm, 0.8 weight %, was added to 97 weight % of purified water in a vessel and stirred at high speed for a minimum of 15 minutes. Sodium chloride, 0.6 weight %,

was then added to the aqueous polymer suspension with stirring.

The resulting suspension was sterilized at 121°C for 45 minutes. The suspension was cooled to about 50°C and 10 N sodium hydroxide solution was then sterile filtered into the suspension with stirring to adjust the pH to 7.6-7.8. Additional purified water was sterile filtered into the suspension with stirring to bring the final formulation weight % to 100 percent. The final aqueous suspension had an osmolality of approximately 270 mOsM, a viscosity of approximately 3600 cps, measured as above, and a pH of about 7.6-7.8.

The above discussion of this invention is directed primarily to preferred embodiments and practices thereof. It will be readily apparent to those skilled in the art that further changes and modifications in the actual implementation of the concepts described herein can easily be made without departing from the spirit and scope of the invention as defined by the following claims.

We Claim:

1. A topical ophthalmic medicament delivery system administrable to the eye in drop form and rapidly gellable in contact with the eye's tear fluid to a substantially greater viscosity than that of the originally-introduced suspension to permit the resulting gel to remain in the eye for a prolonged period of time and release a medicament contained therein in sustained fashion comprising an aqueous suspension containing from about 0.1% to about 6.5% by weight, based on the total weight of said suspension, of a lightly crosslinked carboxyl-containing polymer having a particle size of not more than about 50 μm in equivalent spherical diameter, prepared by polymerizing at least about 50% by weight of one or more carboxyl-containing monoethylenically unsaturated monomers and from about 0.1% to about 5% by weight of a crosslinking agent, said weight percentages of monomers being based on the total weight of monomers polymerized, said suspension being at a pH of from about 3 to about 6.5 and an osmotic pressure of from about 10 to about 400 mOsM and having a viscosity of from about 1,000 to about 30,000 centipoise, as measured at about 25°C using a Brookfield Digital LVT Viscometer equipped with a number 25 spindle and a 13R small sample adapter at 12 rpm.

2. A topical ophthalmic medicament delivery system as in claim 1 containing an ophthalmic medicament.

3. A topical ophthalmic medicament delivery system as in claim 2 in which said polymer has a particle size of not more than about 30 μm.

4. A topical ophthalmic medicament delivery system as in claim 3 in which said polymer is one prepared from at least about 90% by weight of one or more carboxyl-containing monoethylenically unsaturated monomers.

5. A topical ophthalmic medicament delivery system as in claim 2 in which said polymer is one prepared by suspension or emulsion polymerizing acrylic acid and a non-polyalkenyl polyether difunctional crosslinking agent to a particle size of not more than about 50 μm in equivalent spherical diameter.

6. A topical ophthalmic medicament delivery system as in claim 5 in which said crosslinking agent is divinyl glycol.

7. A topical ophthalmic medicament delivery system as in claim 6 in which said osmotic pressure is achieved using a physiologically and ophthalmologically acceptable salt in an amount of from about 0.01% to about 1% by weight, based on the total weight of the suspension.

8. A topical ophthalmic medicament delivery system as in claim 7 in which said salt is sodium chloride.

9. A topical ophthalmic medicament delivery system as in claim 8 in which said medicament is present in an amount of from about 0.005% to about 10% by weight, based on the total weight of the suspension.

10. A topical ophthalmic medicament delivery system as in claim 9 in which said medicament is fluorometholone.

11. A topical ophthalmic medicament delivery system as in claim 9 in which said medicament is pilocarpine.

12. An improved method of delivering a topical ophthalmic medicament to the eye which comprises preparing an aqueous suspension containing from about 0.1% to about 6.5% by weight, based on the total weight of said suspension, of a lightly crosslinked carboxyl-containing polymer having a particle size of not more than about 50 μm in equivalent spherical diameter, prepared by polymerizing at least about 50% by weight of one or more carboxyl-containing monoethylenically unsaturated monomers and from about 0.1% to about 5% by weight of a crosslinking agent, said weight percentages of monomers being based on the total weight of monomers polymerized, said suspension being at a pH of from about 3 to about 6.5 and an osmotic pressure of from about 10 to about 400 mOsM and having a viscosity of from about 1,000 to about 30,000 centipoise, as measured at about 25°C using a Brookfield Digital LVT Viscometer equipped with a number 25 spindle and a 13R small sample adapter at 12 rpm and administering said suspension to the eye in drop form, whereby said suspension rapidly gels in contact with the eye's tear fluid to a substantially greater viscosity than that of the originally-introduced suspension to permit the resulting gel to remain in the eye for a prolonged period of time and release a medicament contained therein in sustained fashion.

13. A method as in claim 12 in which said topical ophthalmic medicament delivery system contains an ophthalmic medicament.

14. A method as in claim 12 in which said polymer has a particle size of not more than about 30μm.

15. A method as in claim 13 in which said polymer is one in which up to about 40% by weight of said carboxy-containing monoethylenically unsaturated monomers has been replaced by one or more non-carboxy-containing monoethylenically unsaturated monomers containing only physiologically and ophthalmologically innocuous substituents.

16. A method as in claim 13 in which said polymer is one prepared by suspension or emulsion polymerizing acrylic acid and a non-polyalkenyl polyether difunctional crosslinking agent to a particle size of not more than about 50 μm in equivalent spherical diameter.

17. A method as in claim 16 in which said crosslinking agent is divinyl glycol.

18. A method as in claim 17 in which said osmotic pressure is achieved using a physiologically and ophthalmologically acceptable salt in an amount of from about 0.01% to about 1% by weight, based on the total weight of the suspension.

19. A method as in claim 18 in which said salt is sodium chloride.

20. A method as in claim 19 in which said medicament is present in an amount of from about 0.005% to about 10% by weight, based on the total weight of the suspension.

21. A method as in claim 20 in which said medicament is fluorometholone.

22. A method as in claim 20 in which said medicament is pilocarpine.

23. A dry eye/tear substitute system administrable to the eye in drop form comprising an aqueous suspension containing from about 0.1% to about 6.5% by weight, based on the total weight of said suspension, of a lightly crosslinked carboxyl-containing polymer having a particle size of not more than about 50 μm in equivalent spherical diameter, prepared by polymerizing at least about 50% by weight of one or more carboxy-containing monoethylenically unsaturated monomers and from about 0.1% to about 5% by weight of a crosslinking agent, said weight percentages of monomers being based on the total weight of monomers polymerized, said suspension being at a pH of from about 5.2 to about 8.0 and an osmotic pressure of from about 10 to about 400 mOsM and having a viscosity of from about 1,000 to about 30,000 centipoise, as measured at about 25°C using a Brookfield Digital LVT Viscometer equipped with a number 25 spindle and a 13R small sample adapter at 12 rpm.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US89/00451

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC INT. CL: 4 IPC(4)
A61K 31/74, A61K 31/78, A01J 21/100, A61K 47/00;
U.S. CL: 424/78,424/81,424/427,514/912,514/913,514/914,514/915

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
US	424/78, 424/81, 424/427, 514/912, 514/913, 514/914 514/915

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
Y	US, A, 4,615,697, 10 OCTOBER 1986. (ROBINSON) SEE COL. 4, LINES 1-10: LINES 24-26; COL. 10, 16-3; LINES 53-62: COL. 12, LINES 34-48; EXAMPLE 11.	1-6,10, 12-17,21,23
Y	US, A, 4,271,143, 02 JUNE 1981, (SCHOENWALD ET AL) SEE COL. 2, LINES 56-68; COL. 3, LINES 1-43; EXAMPLES.	1-2, 7-11, 12-13,18-23
Y	EP, A, 2,007,091, 16 MAY 1979, (TOKO YAKUHIN) SEE ENTIRE DOCUMENT.	1-2,7-9, 12-13,18-20, 23
A	US, A, 4,474,751 02 OCTOBER 1984, (HASLAM ET AL)	1-2, 10-13, 21-23,
A	US, A, 3,947,573, 30 MARCH 1976 (RANKIN)	23
A	US, A, 4,478,818 23 OCTOBER 1984, (SHELL ET AL)	1-2, 10, 12-13, 21, 23

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
29 MARCH 1989	05 MAY 1989
International Searching Authority: ISA/US	Signature of Authorized Officer: CARMEN PILI-CURTIS

Form PCT/ISA/210 (second sheet) (Rev.11-87)